(FILE 'HOME' ENTERED AT 17:19:45 ON 09 OCT 2002)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, EMBASE, BIOSIS, MEDICONF' ENTERED AT 17:20:16 ON 09 OCT 2002

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L1      33495 S MUSCLE? (L) NITRIC OXIDE
L2      25468 S MUSCLE? (S) NITRIC OXIDE
L3       8866 S L1 AND GENE?
L4       8637 S MUSCLE? (S) NITRIC OXIDE SYNTHASE
L5       4973 S L4 AND PY<=1998
L6       1637 DUP REM L5 (3336 DUPLICATES REMOVED)
L7          6 S L6 AND MYOBLAST?
L8      28116 S INDUCIBLE NITRIC OXIDE SYNTHASE
L9      10736 S L8 AND (VECTOR OR DNA OR GENE OR VIR?)
L10      1214 S L9 AND (MYOBLAST OR MUSCLE?)
L11      1214 FOCUS L10 1-
L12       468 S L10 AND GENETIC?
L13       266 DUP REM L12 (202 DUPLICATES REMOVED)
L14       266 FOCUS L13 1-
L15       119 S L13 AND PY<=1998
L16         7 S L15 AND (GENE THERAPY)
L17         7 SORT L16 PY
              E  CHANCELLOR MICHAEL?/AU
L18       238 S E2
L19       218 DUP REM L18 (20 DUPLICATES REMOVED)
L20         6 S L19 AND ((INDUCIBLE NITRIC OXIDE SYNTHASE) OR INOS)
L21         6 SORT L20 PY
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=> d an ti so au ab pi l21 1-6

L21 ANSWER 1 OF 6 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:294623 BIOSIS
TI Direct measurement of basal nitric oxide release with a porphyrinic microsensor following **inducible nitric oxide synthase** gene therapy.
SO Journal of Urology, (May, 1998) Vol. 159, No. 5 SUPPL., pp. 95. Meeting Info.: 93rd Annual Meeting of the American Urological Association, Inc. San Diego, California, USA May 30-June 4, 1998 American Urological Association
. ISSN: 0022-5347.
AU Birder, Lori A.; Kanai, Anthony J.; Tirney, Sean; Huard, Johnny; Mattes, Carol E.; Ozawa, Hideo; Jung, Suk Young; Tzeng, Edith; Kibbe, Melina; Hierholzer, Christian; Simmons, Richard L.; Billiar, Timothy R.; De Groat, William C.; **Chancellor, Michael B.**

L21 ANSWER 2 OF 6 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:294601 BIOSIS
TI Nitric oxide synthase (NOS) gene therapy for erectile dysfunction: Comparison between plasmid, adenovirus and adenovirus transduced myoblast vectors.
SO Journal of Urology, (May, 1998) Vol. 159, No. 5 SUPPL., pp. 90. Meeting Info.: 93rd Annual Meeting of the American Urological Association, Inc. San Diego, California, USA May 30-June 4, 1998 American Urological Association
. ISSN: 0022-5347.
AU Huard, Johnny; Tirney, Sean; Mattes, Carol E.; Watanabe, Toyohiko; Ozawa, Hideo; Yoshimura, Naoki; , Jose Moreno; Birder, Lori A.; Kanai, Anthony J.; Degroat, William C.; Tzeng, Edith; Kibbe, Melina; Hierholzer, Christian; Geller, David A.; Simmons, Richard L.; Billiar, Timothy R.; **Chancellor, Michael B.**

L21 ANSWER 3 OF 6 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:294307 BIOSIS
TI Myoblast injection into the bladder wall: A possible method of modulating detrusor contractility and cell-mediated gene therapy for bladder dysfunction.
SO Journal of Urology, (May, 1998) Vol. 159, No. 5 SUPPL., pp. 16. Meeting Info.: 93rd Annual Meeting of the American Urological Association, Inc. San Diego, California, USA May 30-June 4, 1998 American Urological Association

. ISSN: 0022-5347.
AU Huard, Johnny; Tirney, Sean; Mattes, Carol E.; Ozawa, Hideo; Jung, Suk Young; Watanabe, Toyohiko; Birder, Lori A.; Kanai, Anthony J.; Yoshimura, Naoki; De Groat, William C.; **Chancellor, Michael B.**

L21 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2002 ACS
AN 1999:722933 CAPLUS
DN 131:332126
TI Muscle-derived cell mediated gene delivery for treating muscle- and bone-related injury or dysfunction
SO PCT Int. Appl., 140 pp.
CODEN: PIXXD2
IN **Chancellor, Michael B.**; Huard, Johnny
AB The invention provides muscle-derived cells, preferably myoblasts and muscle-derived stem cells, genetically engineered to contain and express one or more heterologous genes or functional segments of such genes, for delivery of the encoded gene products at or near sites of musculoskeletal, bone, ligament, meniscus, cartilage or genitourinary disease, injury, defect, or dysfunction. Ex vivo myoblast mediated gene delivery of human **inducible nitric oxide synthase**, and
the resulting prodn. of nitric oxide at and around the site of injury, are particularly provided by the invention as a treatment for lower genitourinary tract dysfunctions. Ex vivo gene transfer for the musculoskeletal system includes genes encoding acidic fibroblast growth factor, basic fibroblast growth factor, epidermal growth factor, insulin-like growth factor, platelet derived growth factor, transforming growth factor-.beta., transforming growth factor-.alpha., nerve growth factor and interleukin-1 receptor antagonist protein (IRAP), bone morphogenetic protein (BMPs), cartilage derived morphogenetic protein (CDMPs), vascular endothelial growth factor (VEGF), and sonic hedgehog proteins.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9956785	A2	19991111	WO 1999-US9451	19990430
WO 9956785	A3	20010419		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2330660	AA	19991111	CA 1999-2330660	19990430
AU 9937757	A1	19991123	AU 1999-37757	19990430
EP 1113807	A2	20010711	EP 1999-920202	19990430

R: AT, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

L21 ANSWER 5 OF 6 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:156892 BIOSIS
TI Gene therapy as a potential treatment for BPH: Injection of myoblast-adenovirus transfected with human **inducible nitric oxide synthase** (**iNOS**) into
the proximal urethra.
SO Journal of Urology, (April, 1999) Vol. 161, No. 4 SUPPL., pp. 305. Meeting Info.: 94th Annual Meeting of the American Urological Association, Inc. Dallas, Texas, USA May 1-6, 1999 American Urological Association
. ISSN: 0022-5347.
AU Yokoyama, Teruhiko; Fraser, Matthew O.; Tirney, Sean; Mattes, Carol E.; Watanabe, Toyohiko; Ozawa, Hideo; Yoshimura, Naoki; De Groat, William C.; Billiar, Timothy R.; Huard, Johnny; **Chancellor, Michael B.**

L21 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2002 ACS
AN 2001:287319 CAPLUS
DN 135:221224
TI Nitric oxide synthase gene therapy for erectile dysfunction: comparison of plasmid, adenovirus, and adenovirus-transduced myoblast vectors
SO Molecular Urology (2001), 5(1), 37-43
CODEN: MOURFE; ISSN: 1091-5362

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FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, EMBASE, BIOSIS, MEDICONF' ENTERED AT 17:20:16 ON 09 OCT 2002

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L1        33495 S MUSCLE? (L) NITRIC OXIDE
L2        25468 S MUSCLE? (S) NITRIC OXIDE
L3         8866 S L1 AND GENE?
L4         8637 S MUSCLE? (S) NITRIC OXIDE SYNTHASE
L5         4973 S L4 AND PY<=1998
L6         1637 DUP REM L5 (3336 DUPLICATES REMOVED)
L7            6 S L6 AND MYOBLAST?
L8        28116 S INDUCIBLE NITRIC OXIDE SYNTHASE
L9        10736 S L8 AND (VECTOR OR DNA OR GENE OR VIR?)
L10        1214 S L9 AND (MYOBLAST OR MUSCLE?)
L11        1214 FOCUS L10 1-
L12         468 S L10 AND GENETIC?
L13         266 DUP REM L12 (202 DUPLICATES REMOVED)
L14         266 FOCUS L13 1-
L15         119 S L13 AND PY<=1998
L16           7 S L15 AND (GENE THERAPY)
L17           7 SORT L16 PY

=> d an ti so au ab pi l17 1 3-7

L17  ANSWER 1 OF 7     MEDLINE
AN   96350358     MEDLINE
TI   Vascular inducible nitric oxide
     synthase gene therapy: requirement for
     guanosine triphosphate cyclohydrolase I.
SO   SURGERY, (1996 Aug) 120 (2) 315-21.
     Journal code: 0417347. ISSN: 0039-6060.
AU   Tzeng E; Yoneyama T; Hatakeyama K; Shears L L 2nd; Billiar T R
AB   BACKGROUND: Human inducible nitric oxide
     synthase (iNOS) gene transfer inhibits myointimal
     hyperplasia in vitro. However, unstimulated vascular smooth muscle
     cells (SMC) do not synthesize tetrahydrobiopterin (BH4), an essential
     cofactor for iNOS, which may be an obstacle to successful vascular iNOS
     gene therapy. We investigated the capacity of
     gene transfer of guanosine triphosphate (GTP) cyclohydrolase I
     (GTPCH), the rate-limiting enzyme for BH4 biosynthesis, to supply cofactor
     for iNOS activity. METHODS: A human GTPCH expression plasmid (pCIS-GTPCH)
     was transfected into rat aortic SMC (RAOSMC) and BH4-deficient NIH3T3
     cells engineered to stably express human iNOS (3T3-iNOS). GTPCH activity
     and intracellular biopterins were assessed as a measure of successful
     transfection, and the capacity of GTPCH to reconstitute iNOS activity was
     used to determine whether BH4 was made available to the iNOS protein.
     RESULTS: The pCIS-GTPCH-transfected 3T3 cells had demonstrable GTPCH
     activity as compared with control cells (169.3 +/- 6.6 pmol/hr/mg versus
     0, p < 0.001). Intracellular biopterin levels were also increased in
     transfected 3T3 and SMC (60.6 +/- 2.6 and 101.7 +/- 28.3 pmol/mg,
     respectively, versus less than 4 in control cells). GTPCH reconstituted
     near-maximal iNOS activity in 3T3-iNOS cells despite a gene
     transfer efficiency of less than 1%. GTPCH and iNOS enzymes did not have
     to coexist in the same cell for the synthesized BH4 to support iNOS
     activity. CONCLUSION: GTPCH gene transfer reconstitutes iNOS
     activity in BH4-deficient cells despite poor transfer efficiency. GTPCH
     can deliver a cofactor to targeted cells even if it is synthesized in
     neighboring cells, and may be a means to concurrently deliver BH4 with
     iNOS in vivo.

L17  ANSWER 3 OF 7  CAPLUS  COPYRIGHT 2002 ACS
AN   1997:710292  CAPLUS
DN   127:355315
TI   Adenoviral iNOS gene transfer activates cGMP- and p21-dependent
     antiproliferative pathways in vascular smooth muscle cells
SO   Surgical Forum (1997), 48, 432-433
     CODEN: SUFOAX; ISSN: 0071-8041
AU   Tzeng, Edith; Lizonova, Alena; Kovesdi, Imre; Shears, Larry L., II;
     Billiar, Timothy R.
AB   In rat aortic smooth muscle cells, expts. were carried out to
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detn. the mechanism of inhibition of proliferation by an adenoviral **vector** carrying the human inducible nitric oxide (NO) synthase (iNOS) cDNA. Both cGMP levels and p21 expression appeared to be involved in the antiproliferative actions of iNOS **gene** transfer on smooth **muscle** cells. However, cGMP does not appear to be involved in regulating p21 expression in response to iNOS **gene** transfer.

L17 ANSWER 4 OF 7 MEDLINE
AN 1998410903 MEDLINE
TI Efficient inhibition of intimal hyperplasia by adenovirus-mediated **inducible nitric oxide synthase** **gene** transfer to rats and pigs in vivo.
SO JOURNAL OF THE AMERICAN COLLEGE OF SURGEONS, **(1998 Sep)** 187 (3) 295-306.
Journal code: 9431305. ISSN: 1072-7515.
AU Shears L L 2nd; Kibbe M R; Murdock A D; Billiar T R; Lizonova A; Kovesdi I; Watkins S C; Tzeng E
AB BACKGROUND: Inadequate nitric oxide (NO) availability may underlie vascular smooth **muscle** overgrowth that contributes to vascular occlusive diseases including atherosclerosis and restenosis. NO possesses a number of properties that should inhibit this hyperplastic healing response, such as promoting reendothelialization, preventing platelet and leukocyte adherence, and inhibiting cellular proliferation. STUDY DESIGN: We proposed that shortterm but sustained increases in NO synthesis achieved with inducible NO synthase (iNOS) **gene** transfer at sites of vascular injury would prevent intimal hyperplasia. We constructed an adenoviral **vector**, AdiNOS, carrying the human iNOS cDNA and used it to express iNOS at sites of arterial injury in vivo. RESULTS: AdiNOS-treated cultured vascular smooth **muscle** cells produced up to 100-fold more NO than control cells. In vivo iNOS **gene** transfer, using low concentrations of AdiNOS (2 x 10(6) plaque forming units [PFU]/rat) to injured rat carotid arteries, resulted in a near complete (>95%) reduction in neointima formation even when followed longterm out to 6 weeks post-injury. This protective effect was reversed by the continuous administration of an iNOS selective inhibitor L-N6-(1-iminoethyl)-lysine. However, iNOS **gene** transfer did not lead to regression of preestablished neointimal lesions. In an animal model more relevant to human vascular healing, iNOS **gene** transfer (5 x 10(8) PFU/pig) to injured porcine iliac arteries in vivo was also efficacious, reducing intimal hyperplasia by 51.8%. CONCLUSIONS: These results indicate that shortterm overexpression of the iNOS **gene** initiated at the time of vascular injury is an effective method of locally increasing NO levels to prevent intimal hyperplasia.

L17 ANSWER 5 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:294623 BIOSIS
TI Direct measurement of basal nitric oxide release with a porphyrinic microsensor following **inducible nitric oxide** **synthase gene therapy**.
SO Journal of Urology, **(May, 1998)** Vol. 159, No. 5 SUPPL., pp. 95.
Meeting Info.: 93rd Annual Meeting of the American Urological Association, Inc. San Diego, California, USA May 30-June 4, 1998 American Urological Association
. ISSN: 0022-5347.
AU Birder, Lori A.; Kanai, Anthony J.; Tirney, Sean; Huard, Johnny; Mattes, Carol E.; Ozawa, Hideo; Jung, Suk Young; Tzeng, Edith; Kibbe, Melina; Hierholzer, Christian; Simmons, Richard L.; Billiar, Timothy R.; De Groat, William C.; Chancellor, Michael B.

L17 ANSWER 6 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:294601 BIOSIS
TI Nitric oxide synthase (NOS) **gene therapy** for erectile dysfunction: Comparison between plasmid, adenovirus and adenovirus transduced **myoblast vectors**.
SO Journal of Urology, **(May, 1998)** Vol. 159, No. 5 SUPPL., pp. 90.
Meeting Info.: 93rd Annual Meeting of the American Urological Association, Inc. San Diego, California, USA May 30-June 4, 1998 American Urological Association
. ISSN: 0022-5347.
AU Huard, Johnny; Tirney, Sean; Mattes, Carol E.; Watanabe, Toyohiko; Ozawa,

Hideo; Yoshimura, Naoki; , Jose Moreno; Birder, Lori A.; Kanai, Anthony J.; Degroat, William C.; Tzeng, Edith; Kibbe, Melina; Hierholzer, Christian; Geller, David A.; Simmons, Richard L.; Billiar, Timothy R.; Chancellor, Michael B.

L17 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:294307 BIOSIS
TI **Myoblast** injection into the bladder wall: A possible method of modulating detrusor contractility and cell-mediated **gene therapy** for bladder dysfunction.
SO Journal of Urology, (**May, 1998**) Vol. 159, No. 5 SUPPL., pp. 16. Meeting Info.: 93rd Annual Meeting of the American Urological Association, Inc. San Diego, California, USA May 30-June 4, 1998 American Urological Association
. ISSN: 0022-5347.
AU Huard, Johnny; Tirney, Sean; Mattes, Carol E.; Ozawa, Hideo; Jung, Suk Young; Watanabe, Toyohiko; Birder, Lori A.; Kanai, Anthony J.; Yoshimura, Naoki; De Groat, William C.; Chancellor, Michael B.

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L2        25468 S MUSCLE? (S) NITRIC OXIDE
L3         8866 S L1 AND GENE?
L4         8637 S MUSCLE? (S) NITRIC OXIDE SYNTHASE
L5         4973 S L4 AND PY<=1998
L6         1637 DUP REM L5 (3336 DUPLICATES REMOVED)
L7            6 S L6 AND MYOBLAST?
L8        28116 S INDUCIBLE NITRIC OXIDE SYNTHASE
L9        10736 S L8 AND (VECTOR OR DNA OR GENE OR VIR?)
L10        1214 S L9 AND (MYOBLAST OR MUSCLE?)
L11        1214 FOCUS L10 1-
L12         468 S L10 AND GENETIC?
L13         266 DUP REM L12 (202 DUPLICATES REMOVED)
L14         266 FOCUS L13 1-

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L14  ANSWER 3 OF 266  CAPLUS  COPYRIGHT 2002 ACS
AN   1999:722933  CAPLUS
DN   131:332126
TI   Muscle-derived cell mediated gene delivery for
     treating muscle- and bone-related injury or dysfunction
SO   PCT Int. Appl., 140 pp.
     CODEN: PIXXD2
IN   Chancellor, Michael B.; Huard, Johnny
AB   The invention provides muscle-derived cells, preferably
     myoblasts and muscle-derived stem cells,
     genetically engineered to contain and express one or more
     heterologous genes or functional segments of such genes
     , for delivery of the encoded gene products at or near sites of
     musculoskeletal, bone, ligament, meniscus, cartilage or genitourinary
     disease, injury, defect, or dysfunction.  Ex vivo myoblast
     mediated gene delivery of human inducible
     nitric oxide synthase, and the resulting
     prodn. of nitric oxide at and around the site of injury, are particularly
     provided by the invention as a treatment for lower genitourinary tract
     dysfunctions.  Ex vivo gene transfer for the musculoskeletal
     system includes genes encoding acidic fibroblast growth factor,
     basic fibroblast growth factor, epidermal growth factor, insulin-like
     growth factor, platelet derived growth factor, transforming growth
     factor-.beta., transforming growth factor-.alpha., nerve growth factor and
     interleukin-1 receptor antagonist protein (IRAP), bone morphogenetic
     protein (BMPs), cartilage derived morphogenetic protein (CDMPs), vascular
     endothelial growth factor (VEGF), and sonic hedgehog proteins.
     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
PI   WO 9956785         A2   19991111       WO 1999-US9451   19990430
     WO 9956785         A3   20010419
         W:  AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,
             DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,
             JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,
             MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
             TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD,
             RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
             ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
             CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     CA 2330660         AA   19991111       CA 1999-2330660  19990430
     AU 9937757         A1   19991123       AU 1999-37757    19990430
     EP 1113807         A2   20010711       EP 1999-920202   19990430
         R:  AT, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

L14  ANSWER 4 OF 266  CAPLUS  COPYRIGHT 2002 ACS
AN   1996:176492  CAPLUS
DN   124:227895
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TI Regulation of interleukin-1.beta.-stimulated **inducible nitric oxide synthase** expression in cultured vascular smooth **muscle** cells by hemostatic proteins
SO Biochemical Pharmacology (1996), 51(6), 847-53
CODEN: BCPCA6; ISSN: 0006-2952
AU Durante, William; Kroll, Michael H.; Orloff, Gregory J.; Cunningham, James M.; Scott-Burden, Timothy; Vanhoutte, Paul M.; Schafer, Andrew I.
AB Expts. were performed to examine the mechanism by which specific hemostatic proteins regulate the release of nitric oxide (NO) from interleukin-1.beta. (IL-1.beta.) stimulated cultured rat aortic smooth **muscle** cells. Treatment of smooth **muscle** cells with IL-.beta. stimulated **inducible nitric oxide synthase** (iNOS) mRNA expression, which preceded the release of NO (as measured by the accumulation of nitrite in the culture media). The cytokine-stimulated prodn. of nitrite was blocked by the protein synthesis inhibitor cycloheximide, the transcriptional inhibitor actinomycin D, and the competitive inhibitor of NOS nitro-L-arginine. However, only actinomycin D inhibited IL-1.beta.-stimulated iNOS mRNA expression. Treatment of smooth **muscle** cells with IL-1.beta. in the presence of platelet derived growth factor or thrombin resulted in the inhibition of cytokine-stimulated expression of iNOS mRNA and NO release. The inhibitory effect of thrombin was reversed by hirudin and was mimicked by a 14 amino acid thrombin receptor activating peptide. In contrast, the concomitant exposure of smooth **muscle** cells to IL-1.beta. and plasmin resulted in the potentiation of both IL-1.beta.-stimulated iNOS expression and NO generation. Finally, treatment of smooth **muscle** cells with IL-1.beta. in the presence of the hemostatic proteins did not affect the half-life of iNOS mRNA. These results demonstrate that specific protein components of the hemostatic system regulate IL-1.beta.-stimulated iNOS and mRNA expression in vascular smooth **muscle** cells. The capacity of hemostatic proteins to modulate the induction of vascular iNOS activity may play an important role in governing the release of NO and regulating thrombogenesis in vivo.

L14 ANSWER 7 OF 266 CAPLUS COPYRIGHT 2002 ACS
AN 2001:254592 CAPLUS
DN 134:276480
TI Regulation of **gene** expression in vascular smooth **muscle** cells
SO Jpn. Kokai Tokkyo Koho, 71 pp.
CODEN: JKXXAF
IN Hecker, Markus; Lauth, Manfred; Wagner, Andreas H.
AB A method for the regulation of **gene** transcription in smooth **muscle**, endothelial, or cardiac cells by using double-stranded nucleic acids capable of sequence-specific binding to the **gene** for transcription factor AP-1 or C/EBP. The cells are part of a coronary or peripheral artery vessel or vascular graft. The **gene** or **genes** regulating the proliferation or migration of said cells, are used. An endothelin **gene** (endothelin-1), a macrophage chemotactic protein (MCP) **gene** (MCP-1), and a **inducible nitric oxide synthase** (iNOS) **gene**, in particular are used. Modulation leads to activation or repression of said **gene** or **genes**.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001095573	A2	20010410	JP 1999-261035	19990914

PI

L14 ANSWER 9 OF 266 MEDLINE
AN 1998378108 MEDLINE
TI Molecular cloning and analysis of the rat **inducible nitric oxide synthase gene** promoter in aortic smooth **muscle** cells.
SO BIOCHEMICAL PHARMACOLOGY, (1998 Jun 1) 55 (11) 1873-80.
Journal code: 0101032. ISSN: 0006-2952.
AU Zhang H; Chen X; Teng X; Snead C; Catravas J D
AB We have cloned five **DNA** fragments (-0.32, -0.48, -1.7, -3.2, and -5.1 kb) of the 5'-flanking region of the rat **inducible nitric oxide synthase** (iNOS) **gene** from rat genomic **DNA**. The functional importance of the 5'-flanking region was determined by transient expression of iNOS

promoter-luciferase constructs in cultures of rat aortic smooth **muscle** cells. The -0.48 kb construct, containing one nuclear factor kappaB (NF-kappaB) binding site, expressed basal promoter activity but showed only a 1.5- and 1.7-fold increase in luciferase activity in response to lipopolysaccharide (LPS) or a cytokine mixture, respectively. However, the -3.2 kb construct (containing a second NF-kappaB binding site) showed full promoter activity with a 24-fold increase in response to LPS or cytokine mixture. The -5.1 kb construct showed no further increase in luciferase activity, suggesting that the 1.9 kb upstream of -3.2 kb may not be important in rat iNOS regulation. Rat iNOS promoter induction did not appear to be transcriptionally regulated by NO since NOS inhibitors did not affect induction. These data are in marked contrast to the mouse iNOS promoter in which a **DNA** sequence as short as a -85 bp, containing one NF-kappaB site, confers 10-fold inducibility by LPS. The present findings demonstrate that the rat iNOS **gene** is transcriptionally regulated by cytokines and LPS, but, unlike the mouse **gene**, the downstream NF-kappaB site does not appear to be a key region in responses to cytokines and LPS. These data suggest that the regulation of the rat **gene** may require the coexistence of at least two NF-kappaB sites or other elements upstream of -0.48 kb of the 5'-flanking region.

L18 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS
AN 1999:282116 CAPLUS
DN 130:321233
TI Human **urinary incontinence** and methods of treatment using **IGF-I** or **IGF-II**,
SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2
IN Spencer, E. Martin; Lue, Tom
AB A method is provided for treating human **urinary incontinence** using therapeutic amts. of human insulin-like growth factor-I (**IGF-I**) administered systemically, intraurethrally, or periurethrally. Alteration of the muscles, nerves and fascia of the bladder, urethra and pelvic floor are the most important factors in the development of **urinary incontinence**. These alterations may occur in women subsequent to vaginal delivery and may be caused in both sexes by trauma and degeneration. **IGF-I** significantly decreases the incidence of **urinary incontinence** in exptl. models by its favorable actions on muscle tissues, nervous tissues, and pelvic fascia, in combination or individually. Administering a complex of an IGF with one of the IGF binding proteins may provide a better response than **IGF-I** alone. Growth hormone may also be effective by virtue of its stimulatory actions on **IGF-I** and IGF binding protein-3, and possibly by an independent action on tissue repair.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9920299	A1	19990429	WO 1998-US21919	19981016
W: GD				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

L18 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS
AN 1998:542993 CAPLUS
DN 129:157327
TI Treatment for **urinary incontinence** using gene therapy techniques
SO PCT Int. Appl., 118 pp.
CODEN: PIXXD2
IN Coleman, Michael
AB The invention is directed in part towards methods of treating **urinary incontinence** using gene therapy techniques. The methods provide for the delivery and expression of growth factors or neurotrophic factors in mammalian tissues.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9833529	A1	19980806	WO 1998-US2051	19980204
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9861427	A1	19980825	AU 1998-61427	19980204
AU 739224	B2	20011004		
EP 981378	A1	20000301	EP 1998-906110	19980204
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001511154	T2	20010807	JP 1998-533206	19980204

L26 ANSWER 5 OF 160 CAPLUS COPYRIGHT 2002 ACS
AN 1995:849459 CAPLUS
DN 123:247693
TI Treatment of arthritic and post-surgical orthopedic conditions with **Insulin-like** Growth Factor-I
SO U.S., 4 pp.
CODEN: USXXAM
IN Dipasquale, Gene
AB A method is disclosed for reducing **atrophy** in at least one striated skeletal **muscle** of an individual. The method comprises administering a therapeutically effective amt. of **insulin-like** growth factor-I (**IGF-I**) to the individual.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5444047	A	19950822	US 1994-261849	19940616

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     (FILE 'HOME' ENTERED AT 13:33:38 ON 16 MAY 2002)

     FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, BIOSIS, MEDICONF'
     ENTERED AT 13:33:46 ON 16 MAY 2002
L1       243463 S IGF-I OR IGF-II OR PDGF OR EGF OR NGF OR BDNF OR IL-15 OR NT-
L2       125929 S L1 AND (URETHRAL SPHINCTER) OR DETRUSOR OR PELVIC
L3           48 S L2 AND (GENE THERAPY)
L4           29 DUP REM L3 (19 DUPLICATES REMOVED)
L5           29 SORT L4 PY
L6           98 S L2 AND PROMOTER
L7           34 DUP REM L6 (64 DUPLICATES REMOVED)
L8           34 FOCUS L7 1-
L9         9384 S L1 AND PROMOTER
L10         564 S L1 AND ((MYOGENIC OR MUSCLE) (L) PROMOTER)
L11           6 S L10 AND (URETHRAL OR SPHINCTER OR DETRUSOR OR PELVIC)
L12           2 DUP REM L11 (4 DUPLICATES REMOVED)
L13           8 S L1 AND (URINARY INCONTINENCE)
L14           6 DUP REM L13 (2 DUPLICATES REMOVED)
L15           6 SORT L14 PY
L16       28490 S URINARY INCONTINENCE
L17           2 S L16 AND (IGF-I OR IGF-II)
L18           2 DUP REM L17 (0 DUPLICATES REMOVED)
L19      109681 S IGF-I OR IGF-II OR (INSULIN LIKE)
L20         233 S L19 AND (PERIPHERAL NERVE)
L21         120 DUP REM L20 (113 DUPLICATES REMOVED)
L22         120 FOCUS L21 1-
L23         669 S L19 AND ATROPH?
L24         325 S L23 AND MUSCLE
L25         160 DUP REM L24 (165 DUPLICATES REMOVED)
L26         160 FOCUS L25 1-
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AU Tirney, Sean; Mattes, Carol E.; Yoshimura, Naoki; Yokayama, Teruhiko; Ozawa, Hideo; Tzeng, Edith; Birder, Lorie A.; Kanai, Anthony J.; Huard, Johnny; De Groat, William C.; **Chancellor, Michael B.**

AB Background and Purpose: Nitric oxide (NO) has been recognized as an important transmitter for genitourinary tract function. This transmitter mediates smooth muscle relaxation and is essential for erection. The objective of our research was to det. whether overexpression of nitric oxide synthase (NOS) in the corpus cavernosum of the penis would correct erectile dysfunction. Materials and Methods: We introduced the inducible form of the enzyme NOS (**iNOS**) into the corpus cavernosum of adult (250-300 g) male Sprague-Dawley rats by injecting a soln. of plasmid, adenovirus, or adenovirus-transduced myoblast cells (adeno-myoblast) (N = 3-5 each group). We also injected plasmid, adenovirus, and adeno-myoblast encoding the expression of the .beta.-gatactosidase reporter gene. Results: We noted expression of .beta.-galactosidase throughout the corpora cavernosum after injection of each of the three solns. Staining was greatest for adeno-myoblast followed by adenovirus and then plasmid. The basal intracavernous pressure (ICP) of **iNOS**-treated animals (adenovirus and adenovirus-transduced myoblast) increased to 55.+-.23 cm H2O .nu. 5.+-.6 H2O in naive animals (P = 0.001). Stimulation of the cavernous nerve (15 Hz, 1.5 ms, 10-40 V, 1 min) resulted in a twofold increase in ICP (adenovirus and adenomyoblast) from the basal level of the **iNOS** -treated animals. Direct in situ measurement of NO demonstrated release of 1 to 1.3 .mu.M NO in the adeno-myoblast-treated penis. Conclusion: Myoblast-mediated gene therapy was more successful in delivering **iNOS** into the corpus cavernosum than were the direct adenovirus or plasmid transfection methods. Gene therapy of NOS may open new avenues of treatment for erectile dysfunction. Control of NOS expression would be necessary to prevent priapism.

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L Number	Hits	Search Text	DB	Time stamp
12	3691	urinary ADJ incontinence	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/09 17:59
19	2	(urinary ADJ incontinence) and (inducible ADJ nitric ADJ oxide)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/09 18:09
26	4229	urinary WITH incontinence	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/09 17:59
33	6	(urinary WITH incontinence) and (inducible ADJ nitric ADJ oxide)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/09 17:59
51	3	CHANCELLOR ADJ MICHAEL	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/09 18:06
60	507	inducible ADJ nitric ADJ oxide	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/09 18:09
67	75	(inducible ADJ nitric ADJ oxide) and (gene ADJ therapy)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/09 18:10
74	16	(US-5942496-$ or US-5763416-$ or US-5466676-$ or US-6271211-$ or US-5068224-$ or US-5444047-$ or US-5739113-$ or US-6447768-$ or US-6133281-$).did. or (WO-9833529-$ or WO-9824922-$ or WO-9956785-$ or WO-9600006-$).did. or (US-20010041355-$ or US-6239117-$ or WO-200037124-$ or US-5658565-$).did.	USPAT; EPO; DERWENT	2002/10/09 18:15
78	5	((US-5942496-$ or US-5763416-$ or US-5466676-$ or US-6271211-$ or US-5068224-$ or US-5444047-$ or US-5739113-$ or US-6447768-$ or US-6133281-$).did. or (WO-9833529-$ or WO-9824922-$ or WO-9956785-$ or WO-9600006-$).did. or (US-20010041355-$ or US-6239117-$ or WO-200037124-$ or US-5658565-$).did.) and (inducible ADJ nitric ADJ oxide)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/10/09 18:16
-	36	(urinary ADJ incontinence) and (gene ADJ therapy)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/09 18:09
-	7	(US-5763416-$ or US-5942496-$ or US-6239117-$ or US-6271211-$).did. or (WO-9833529-$).did. or (US-6239117-$ or WO-200037124-$ or US-20010041355-$).did.	USPAT; EPO; DERWENT	2002/05/15 17:14
-	10	COLEMAN-MICHAEL	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/09 18:06

-	10	(US-5942496-$ or US-5763416-$ or US-6271211-$ or US-6239117-$ or US-5068224-$ or US-5444047-$).did. or (WO-9833529-$ or WO-9824922-$).did. or (US-20010041355-$ or US-6239117-$ or WO-200037124-$).did.	USPAT; EPO; DERWENT	2002/05/16 14:20
-	157	(IGF-I or IGF-II or (insulin ADJ like)) and (URETHERA$1 OR SPHINCTER OR DETRUSOR OR PELVIC)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/05/16 14:23
-	33	((IGF-I or IGF-II or (insulin ADJ like)) and (URETHERA$1 OR SPHINCTER OR DETRUSOR OR PELVIC)) and ((atrophy or atrophied or dysfunction) SAME (muscle or muscular))	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/05/16 14:26

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A2

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(30) Priority Data:
60/083,917 1 May 1998 (01.05.98) US

(71) Applicant: UNIVERSITY OF PITTSBURGH [US/US]; 911 William Pitt Union, Pittsburgh, PA 15260 (US).

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: MUSCLE-DERIVED CELL MEDIATED GENE DELIVERY FOR TREATING MUSCLE- AND BONE-RELATED INJURY OR DYSFUNCTION

(57) Abstract

The present invention provides muscle-derived cells, preferably myoblasts and muscle-derived stem cells, genetically engineered to contain and express one or more heterologous genes or functional segments of such genes, for delivery of the encoded gene products at or near sites of musculoskeletal, bone, ligament, meniscus, cartilage or genitourinary disease, injury, defect, or dysfunction. *Ex vivo* myoblast mediated gene delivery of human inducible nitric oxide synthase, and the resulting production of nitric oxide at and around the site of injury, are particularly provided by the invention as a treatment for lower genitourinary tract dysfunctions. *Ex vivo* gene transfer for the musculoskeletal system includes genes encoding acidic fibroblast growth factor, basic fibroblast growth factor, epidermal growth factor, insulin-like growth factor, platelet derived growth factor, transforming growth factor-β, transforming growth factor-α, nerve growth factor and interleukin-1 receptor antagonist protein (IRAP), bone morphogenetic protein (BMPs), cartilage derived morphogenetic protein (CDMPs), vascular endothelial growth factor (VEGF), and sonic hedgehog proteins.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US98/02051

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(30) Priority Data:
60/036,862 4 February 1997 (04.02.97) US

(71) Applicant *(for all designated States except US)*: GENEMEDICINE, INC. [US/US]; 8301 New Trails Drive, The Woodlands, TX 77381-4248 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: COLEMAN, Michael [US/US]; 50 South Havenridge Drive, The Woodlands, TX 77381 (US).

(74) Agents: WARBURG, Richard, J. et al.; Lyon & Lyon LLP, Suite 4700, 633 West Fifth Street, Los Angeles, CA 90071-2066 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: TREATMENT FOR URINARY INCONTINENCE USING GENE THERAPY TECHNIQUES

(57) Abstract

The invention is directed in part towards methods of treating urinary incontinence using gene therapy techniques. The methods provide for the delivery and expression of growth factors or neurotrophic factors in mammalian tissues.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/85, C07K 14/65, A61K 48/00, A01K 67/027

A1

(11) International Publication Number: WO 98/24922

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(21) International Application Number: PCT/US97/21852

(22) International Filing Date: 1 December 1997 (01.12.97)

(30) Priority Data:
60/031,539 2 December 1996 (02.12.96) US
08/974,572 19 November 1997 (19.11.97) US

(71) Applicants: GENEMEDICINE, INC. [US/US]; 8301 New Trails Drive, The Woodlands, TX 77381-4248 (US). BAYLOR COLLEGE OF MEDICINE [US/US]; Texas Medical Center, One Baylor Plaza, Houston, TX 77030-3498 (US).

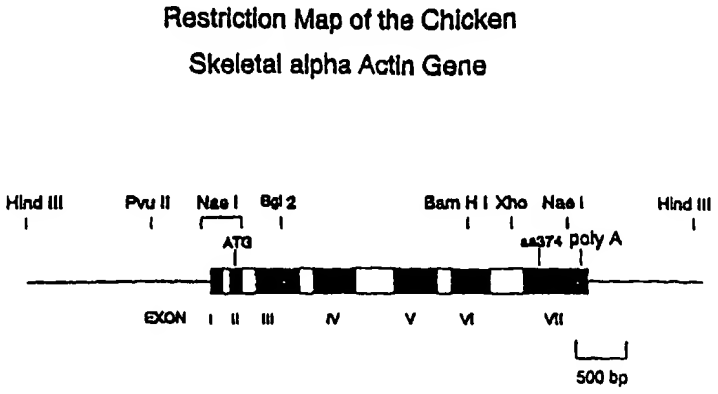
(72) Inventors: COLEMAN, Michael; 50 South Havenridge Drive, The Woodlands, TX 77381 (US). SCHWARTZ, Robert; 4019 Marlowe, Houston, TX 77005 (US). DEMAYO, Francesco, J.; 3626 Merrick, Houston, TX 77025 (US).

(74) Agents: WARBURG, Richard, J. et al.; Lyon & Lyon LLP, Suite 4700, 633 West Fifth Street, Los Angeles, CA 90071-2066 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: INSULIN-LIKE GROWTH FACTOR I (IGF-I) EXPRESSION SYSTEM AND METHODS OF USE



(57) Abstract

This invention relates to gene delivery and expression, including gene therapy, by using vectors which encode stable mRNA and methods of using such vectors. In particular, this invention relates to vectors which establish controlled expression of recombinant IGF-I genes within tissues at certain levels. The vector includes a 5' flanking region which includes necessary sequences for expression of a nucleic acid cassette, a 3' flanking region including a 3' UTR and/or 3' NCR, and a linker which connects the 5' flanking region to a nucleic acid sequence. The linker has a position for inserting a nucleic acid cassette. The linker does not contain the coding sequence of a gene that the linker is naturally associated with. The 3' flanking region is 3' to the position for inserting the nucleic acid cassette. The expression vectors of the present invention can also be regulated by a regulatory system and/or constructed with a coating.